General

Guideline Title

Management of patients with refractory angina: Canadian Cardiovascular Society/Canadian Pain Society joint guidelines.

Bibliographic Source(s)

McGillion M, Arthur HM, Cook A, Carroll SL, Victor JC, L'Allier PL, Jolicoeur EM, Svorkdal N, Niznick J, Teoh K, Cosman T, Sessle B, Watt-Watson J, Clark A, Taenzer P, Coyte P, Malysh L, Galte C, Stone J, Canadian Cardiovascular Society, Canadian Pain Society. Management of patients with refractory angina: Canadian Cardiovascular Society/Canadian Pain Society joint guidelines. Can J Cardiol. 2012 Mar-Apr;28(2 Suppl):S20-41. [182 references] PubMed

Guideline Status

This is the current release of the guideline.

Recommendations

Major Recommendations

The grading of evidence (High, Medium, Low, and, Very Low) and strength of recommendations (Strong or Weak) are defined at the end of the "Major Recommendations" field.

Invasive Therapies

Transmyocardial Laser Revascularization (TMLR)

- Despite some observed improvements in pain and physical limitations, TMLR is associated with significant early postoperative mortality risk and is not recommended (Strong Recommendation, High-Quality Evidence).
- Values and preferences. This recommendation places a high value on patient safety, recognizing that some patients still undergo TMLR, where available (i.e., international centres).

Percutaneous Myocardial Laser Revascularization (PMLR)

- PMLR may be considered for reduction in the perceived severity of angina pain symptoms (Weak Recommendation, Moderate-Quality Evidence).
- PMLR may be considered for improvement in aspects of health-related quality of life (HRQL) (Weak Recommendation, Moderate-Quality Evidence).
- PMLR is not associated with significant increase in all-cause mortality compared with medical management up to 1 year post intervention (Weak Recommendation, Moderate-Quality Evidence).

- Values and preferences. These recommendations recognize that some patients may choose to pursue PMLR, where available (i.e., international centres) and balance improvement in symptoms and aspects of HRQL with procedural risk.

Spinal Cord Stimulation (SCS)

- SCS may be considered for improving exercise capacity (Weak Recommendation, Moderate-Quality Evidence).
- SCS may be considered for improving HRQL (Weak Recommendation, Moderate-Quality Evidence).
- Values and preferences. These recommendations place a high value on the results of multiple randomized controlled trials (RCT) and a meta-analysis reporting significant improvements, exercise capacity and HRQL outcomes.

Noninvasive Therapies

Enhanced External Counter-pulsation (EECP)

- EECP may be considered for improvements in aspects of HRQL (Weak Recommendation, Low-Quality Evidence).
- EECP may be considered for improvement in severity of angina symptoms (Weak Recommendation, Low-Quality Evidence).
- Values and preferences. These recommendations place a high value on the decision of individual patients to pursue symptom relief and improvements in HRQL outcomes.

Cognitive-behavioural Self-management Interventions

- Self-management training may be considered for reduction in angina pain symptoms and related use of sublingual (SL) nitrates (Weak Recommendation, Moderate-Quality Evidence).
- Self-management training may be considered for improvements in HRQL (Weak Recommendation, Moderate-Quality Evidence).
- Values and preferences. These recommendations place a high value on addressing cognitive and behavioural responses to improve symptoms and HRQL outcomes.

Pharmacologic Therapies

Metabolic Agents

Allopurinol

- More robust RCTs are needed before allopurinol can be recommended as an anti-anginal agent for refractory angina (RFA) patients (Strong Recommendation, Very Low-Quality Evidence).
- Values and preferences. This recommendation recognizes the potential benefits of allopurinol and the need for high-quality, RFA-specific evidence to support future practice recommendations.

Ranolazine

- Robust RCTs focused on patients with RFA are needed before ranolazine can be recommended definitively as an anti-anginal agent (Strong Recommendation, Moderate-Quality Evidence).
- Ranolazine may hold promise for reduction in angina symptoms, particularly for those patients who cannot tolerate upward titration of conventional anti-anginal agents due to depressive effects on heart rate and blood pressure (Weak Recommendation, Moderate-Quality Evidence).
- Values and preferences. The recommendations place a high value on the need for high-quality, RFA-specific evidence to support future practice recommendations, as well as the potential benefit of ranolazine to reduce angina symptoms, particularly among those who cannot tolerate upward titration of conventional anti-anginal agents.

Trimetazidine

- Robust, adequately powered RCTs with long-term follow up are needed to more definitively examine the anti-anginal effects, mortality risk, and adverse events associated with trimetazidine before it can be recommended for the treatment of RFA (Strong Recommendation, Very Low-Quality Evidence).
- Values and preferences. This recommendation places a high value on patient safety and the need for high-quality, RFA-specific evidence to support future practice recommendations.

Nicorandil

- Robust RCTs are needed to examine the effectiveness of nicorandil for RFA patients before specific recommendations can be made (Strong

recommendation, Very Low-Quality Evidence).
- Values and preferences. This recommendation recognizes the potential benefits of nicorandil and the need for high-quality, RFA-specific evidence to support future practice recommendations.

Heart Rate Modulating Agent

Ivabradine

- Robust RCTs focused on patients with RFA are needed before ivabradine can be recommended definitively (Strong Recommendation, Moderate-Quality Evidence).
- Ivabradine may have potential for future use to reduce angina symptoms and SL nitrate consumption, as well as to improve exercise tolerance (Strong Recommendation, Moderate-Quality Evidence).
- Ivabradine may reduce the occurrence of major adverse cardiac events for patients with limiting angina symptoms and left ventricular systolic dysfunction (Weak Recommendation, Moderate-Quality Evidence).
- Values and preferences. These recommendations place a high value on the potential of ivabradine to improve symptoms and exercise tolerance, as well as reduce the occurrence of major adverse cardiac events. The need for high-quality, RFA-specific evidence to support future practice recommendations is also recognized.

Intermittent Thrombolytic Agents

- Robust RCTs are needed to examine the effectiveness and safety of intermittent thrombolysis for RFA patients before recommendations can be made (Strong Recommendation, Very Low-Quality Evidence).
- Values and preferences. This recommendation places a high value on patient safety.

Final Summary Recommendation

- The use of the term 'refractory angina' is recommended as opposed to the term 'no option angina' (or similar terms).
- Effective care of patients with RFA requires an integrated understanding of the underlying ischemic and neural pain mechanisms involved. As such, the collaboration of cardiovascular and pain experts is critical for comprehensive patient assessment and management.
- More RCTs, employing robust methods, are needed. Particular attention should be paid to the use of standardized outcome measures (for comparison across trials), patient-centered outcomes, as well as stricter inclusion criteria, exclusive to those meeting the definition of RFA.
- It is recommended that a working group be struck to examine (1) existing infrastructure, (2) access to care issues, and (3) feasibility, costs, and potential benefits of specialized, multidisciplinary centers of care for RFA.
- Values and preferences. These final summary recommendations place a high value on patient-centered outcomes such as symptom reduction and improvements in HRQL, as well as addressing current gaps in health care for people living with RFA.

Definitions:

Grading of Evidence

High: Further research is very unlikely to change confidence in the estimate of effect.

Moderate: Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.

Low: Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.

Very Low: Any estimate of effect is very uncertain.

Strength of Recommendations

Strong: The desirable effects of an intervention clearly out-weigh the undesirable effects, or clearly do not.

Weak: The trade-offs are less certain — either because of low-quality evidence or because evidence suggests that desirable and undesirable effects are closely balanced.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Refractory angina (RFA)

Note: RFA is a persistent, painful condition characterized by the presence of angina caused by coronary insufficiency in the presence of coronary artery disease which cannot be controlled by a combination of medical therapy, angioplasty/percutaneous interventions, and coronary bypass surgery. While the presence of reversible myocardial ischemia must be clinically established to be the root cause, the pain experienced may arise or persist with or without this ischemia. Chronic is defined as persisting for more than 3 months.

Guideline Category

Management

Treatment

Clinical Specialty

Cardiology

Family Practice

Internal Medicine

Intended Users

Advanced Practice Nurses

Allied Health Personnel

Nurses

Patients

Physician Assistants

Physicians

Guideline Objective(s)

To make practice recommendations about treatment options for refractory angina (RFA) that are based on the best available evidence

Target Population

Patients with refractory angina (RFA)

Interventions and Practices Considered

1. Invasive therapies:
    - Percutaneous myocardial laser revascularization (PMLR)
    - Spinal cord stimulation (SCS)
2. Noninvasive therapies:

    - Enhanced external counter-pulsation (EECP)
    - Cognitive-behavioural self-management
3. Pharmacologic therapies:
    - Metabolic agents (ranolazine)
    - Heart-modulating agents (ivabradine)

Note: The following were considered but not recommended: transmyocardial laser revascularization (TMLR); metabolic agents such as allopurinol, trimetazidine, and nicorandil; and intermittent thrombolytic agents.

Major Outcomes Considered

- Pain
- Nitrate use
- Health-related quality of life
- Morbidity (myocardial infarction, heart transplant, cerebrovascular events, other cardiac events, associated hospitalizations)
- Exercise tolerance
- Mortality

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Searches of Unpublished Data

Description of Methods Used to Collect/Select the Evidence

Search Methods for Identification of Studies

The authors searched CENTRAL, MEDLINE, PubMed, CINHAL, EMBASE, Proquest Dissertation Abstracts, PsycINFO and HealthStar (Jan 1990–June 2010) using combinations of key medical subject heading (MeSH) terms determined in consultation with an external information specialist; hand searches were also conducted of relevant journals, proceedings of major conferences, and secondary references. Experts in the field were also consulted for additional sources such a grey literature and unpublished studies. Authors were contacted where possible to obtain missing information. The search strategy was critiqued and replicated by the external information specialist to ensure comprehensiveness. During the phase of information synthesis, the search process was repeated twice for CENTRAL and monthly for the other databases. Any relevant research protocols in progress, such as Cochrane review protocols, identified during the search process were revisited during the final stages of guideline development. If any such protocols were completed and published, following June 2010, the authors considered them for inclusion in the analyses.

Final Selection of Studies

The Chairs and Coordinators met regularly to reach consensus on all studies to be included in these guidelines according to the inclusion criteria specified *a priori*. The Chair and Coordinators independently extracted process and outcome data from primary studies that were not already included in meta-analyses or meta-syntheses via an adaptation of a standardized Cochrane-based format used in prior syntheses. This process was reviewed at regular team meetings.

Inclusion Criteria

Types of Studies

Included studies were a) all quantitative systematic reviews and qualitative meta-syntheses, b) randomized controlled trials (RCTs) of interventions for the treatment of refractory angina (RFA) that have not been previously included in systematic reviews, and c) other studies with a comparison group including quasi-RCTs and non-randomized controlled clinical trials (CCTs). Observational/descriptive, retrospective, and case studies or series did not meet the threshold for inclusion for appraisal via Grading of Recommendations Assessment, Development and Evaluation (GRADE) or the generation of practice recommendations.

Types of Patients

Included patients were persons living with RFA, defined as a chronic disease characterized by the presence of persistent, moderate-severe unremitting angina pain resistant to all conventional treatments for coronary artery disease (CAD) and myocardial ischemia including combinations of medical therapy, percutaneous coronary interventions, and coronary artery bypass grafting. The presence of CAD should also have been clinically established as the original cause of the RFA pain.

Types of Interventions

Types of interventions reviewed included the following recognized RFA therapies: laser revascularization techniques, spinal cord stimulation, enhanced external counter-pulsation, self-management training, cardiac sympathectomies, and opioid therapies. The following emerging interventions were also reviewed: metabolic and heart rate modulating agents, intermittent thrombolytic agents, therapeutic angiogenesis, chronic total occlusion percutaneous interventions, coronary sinus reduction devices, shock wave therapy, and myocardial cryotherapy. In cases where there was sufficient evidence pertaining to the effectiveness of interventions, the authors have presented formal practice recommendations. New recommendations will be added to future iterations of these guidelines as evidence is accrued for emerging interventions.

Types of Outcome Measures

The authors focused the systematic review and meta-analyses on the following patient-centered outcomes: pain, nitrate use, health-related quality of life, morbidity (myocardial infarction, heart transplant, cerebrovascular events, other cardiac events and associated hospitalizations), exercise tolerance and mortality. Practice recommendations were generated with respect to these patient-centered outcomes only. Evidence pertaining to mechanistic outcomes, or surrogate outcomes of myocardial perfusion, were not included. Examples of such outcomes include coronary diastolic pressure and flow velocity; myocardial oxygen consumption; arterial stiffness; left ventricular afterload and ejection fraction; myocardial ischemic burden; hemodynamic parameters including coronary perfusion pressure, and pulmonary capillary wedge pressure; endothelial function; and serum protein markers.

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Grading of Evidence

High: Further research is very unlikely to change confidence in the estimate of effect.

Moderate: Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.

Low: Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.

Very Low: Any estimate of effect is very uncertain.

Methods Used to Analyze the Evidence

Meta-Analysis

Systematic Review

Description of the Methods Used to Analyze the Evidence

Appraisal of Methodologic Quality

Quantitative Studies

The authors assessed randomized controlled trials (RCTs) and controlled clinical trials (CCTs) for sample size, clarity of inclusion/exclusion criteria and description of participants, sampling and recruitment methods, generation of randomization sequence, allocation concealment, standardized intervention delivery, reliability and validity of measurement instruments and response rate (RR), blinding of outcome assessment, and examination of group differences, as applicable.

Qualitative Studies

The authors searched for qualitative studies of refractory angina (RFA) interventions that met the criteria set by the National Critical Appraisal Skills Program (CASP) for Qualitative Methodologies including appropriateness of research design, recruitment strategy, data collection methods, reflexivity, ethical issues, rigour of data analysis, and clarity and value of the findings. None were found.

Data Synthesis and Analysis

Primary studies meeting inclusion criteria and not previously contained in meta-analyses were categorized and synthesized based on intervention.

Quantitative Studies

Studies evaluating similar interventions were analyzed using standard meta-analytic techniques. Continuous outcomes were summarized using standardized mean differences (SMD) as an indicator of effect size (ES). SMDs were determined using differences in change over baseline at the end of treatment across treatment groups, divided by the pooled standard deviation. If change over baseline was unavailable, differences in mean values at the end of treatment were used. For studies reporting only medians and inter-quartile ranges (IQR) for continuous outcomes, the authors planned to estimate means and standard deviations (SD) using the method outlined by Hozo et al. (2005); Tomilson and Beyene (2004) have suggested that omission of studies reporting only medians and IQRs may lead to a loss of important information. An SMD of 0.20 SD units was considered a small difference between the experimental and control groups, an SMD of 0.50 a moderate difference, and 0.80 a large difference. Binary outcomes were expressed as odds ratios. The authors used standard inverse-variance random-effects meta-analysis to combine the trials.

Heterogeneity between trials was evaluated using Chi-squared tests for the Tau-squared statistic, and quantified using the I^2 statistic, which describes the percentage of variation across trials that is attributable to heterogeneity rather than to chance. I^2 values of 25%, 50%, and 75% may be considered as indicators of low, moderate, and high heterogeneity, although this has been shown to depend on the size and number of trials included. In instances where significant heterogeneity might be found, the authors planned to conduct sensitivity analyses removing studies, such as those with estimated mean values or those of lower methodological quality, in order to determine factors related to the heterogeneity and the effect on the pooled outcome.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

These guidelines are predicated upon a 2009 Canadian Cardiovascular Society (CCS) Position Statement which identified that underlying the problem of refractory angina (RFA) management is the lack of a formalized, coordinated, inter-professional strategy between the cardiovascular and pain science/clinical communities. The guidelines are therefore a joint initiative of the CCS and the Canadian Pain Society (CPS) and were developed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system of evidence evaluation, in order to make practice recommendations about treatment options for RFA that are based on the best available evidence.

Rating Scheme for the Strength of the Recommendations

Strength of Recommendations

Strong: The desirable effects of an intervention clearly outweigh the undesirable effects, or clearly do not.

Weak: The trade-offs are less certain — either because of low-quality evidence or because evidence suggests that desirable and undesirable effects are closely balanced.

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Not stated

Description of Method of Guideline Validation

Not applicable

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Safe and effective management of patients with refractory angina

Potential Harms

- In one study, minor adverse events (e.g., skin abrasions, and leg and back pain) related to enhanced external counter-pulsation (EECP) were reported by 55% of the treatment group, compared with 20% in the sham group.
- Complications of spinal cord stimulation (SCS) reported include lead dislodgement, electrode fracture, and subcutaneous infections. Periprocedural complications are rare as the electrodes are inserted percutaneously. Treatment is not suitable for patients who have diseases of the spinal column or have cognitive impairment precluding safe use of an external programming device.
- Ivabradine was well tolerated, with minor visual disturbances (i.e., phosphenes) being the most frequently reported adverse effect. Ivabradine may reduce the occurrence of major adverse cardiac events for patients with limiting angina symptoms and left ventricular systolic dysfunction.

Contraindications

Contraindications

- Enhanced external counter-pulsation (EECP) is contraindicated for persons with arrhythmias that interfere with the device triggering mechanism, bleeding diathesis, active thrombophlebitis, peripheral vascular disease, aortic aneurysm, or aortic stenosis, uncontrolled hypertension (i.e., 180/110), severe lower extremity arterial-occlusive disease, uncontrolled congestive heart failure, and pregnancy.
- Contraindications of ranolazine include pregnancy, breastfeeding, and history of allergy.

Qualifying Statements

Qualifying Statements

This statement was developed following a thorough consideration of medical literature and the best available evidence and clinical experience. It represents the consensus of a Canadian panel comprised of multidisciplinary experts on this topic with a mandate to formulate disease-specific recommendations. These recommendations are aimed to provide a reasonable and practical approach to care for specialists and allied health professionals obliged with the duty of bestowing optimal care to patients and families, and can be subject to change as scientific knowledge and technology advance and as practice patterns evolve. The statement is not intended to be a substitute for physicians using their individual judgement in managing clinical care in consultation with the patient, with appropriate regard to all the individual circumstances of the patient, diagnostic and treatment options available and available resources. Adherence to these recommendations will not necessarily produce successful outcomes in every case.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

Staying Healthy

IOM Domain

Effectiveness

Patient-centeredness

Safety

Identifying Information and Availability

Bibliographic Source(s)

McGillion M, Arthur HM, Cook A, Carroll SL, Victor JC, L'Allier PL, Jolicoeur EM, Svorkdal N, Niznick J, Teoh K, Cosman T, Sessle B,

Watt-Watson J, Clark A, Taenzer P, Coyte P, Malysh L, Galte C, Stone J, Canadian Cardiovascular Society, Canadian Pain Society. Management of patients with refractory angina: Canadian Cardiovascular Society/Canadian Pain Society joint guidelines. Can J Cardiol. 2012 Mar-Apr;28(2 Suppl):S20-41. [182 references] PubMed

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2012 Mar-Apr

Guideline Developer(s)

Canadian Cardiovascular Society - Professional Association

Canadian Pain Society - Professional Association

Source(s) of Funding

These guidelines were funded by the Canadian Institutes of Health Research, #188445.

Publication and distribution of this article are supported by Servier Canada and the Heart and Stroke Foundation of Ontario.

Guideline Committee

Not stated

Composition of Group That Authored the Guideline

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Financial Disclosures/Conflicts of Interest

M.M. and H.M.A. have received honoraria/consulting fees from Servier. P.L.L. has received honoraria/consulting fees from AstraZeneca, Sanofi-Aventis, Eli Lilly, Merck Schering, Novartis, and Pfizer. E.M.J. has received honoraria/consulting fees from Gilead, Servier Canada, Lilly, and AstraZeneca and participated in clinical trials sponsored by Gilead, AstraZeneca, GlaxoSmithKline, and Neovasc Inc. N.S. has received honoraria/consulting fees from Medtronic. J.N. has received honoraria/consulting fees from Merck-Frosst, Schering, AstraZeneca, Sanofi, Pfizer, and Boehringer-Ingelheim and received website sponsorship and clinical prevention program support from Merck-Frosst, Schering, AstraZeneca,

Sanofi, Pfizer, and Boehringer-Ingelheim. B.S. has received honoraria/consulting fees from Pfizer Canada and Lilly Canada and received a research grant from Pfizer Canada. L.M. has received honoraria/consulting fees from Medtronic of Canada and Boston Scientific. C.G. has received lecturing honoraria from Sanofi-Aventis and Boston Scientific. J.S. has received honoraria/consulting fees from AstraZeneca, Merck-Frosst, Pfizer, Schering, Novartis, and GlaxoSmithKline. The other authors had no conflicts of interest to disclose.

Guideline Status

This is the current release of the guideline.

Guideline Availability

Electronic copies: Available in Portable Document Format (PDF) from the Canadian Journal of Cardiology Web site .

Availability of Companion Documents

None available

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on May 9, 2013. The information was verified by the guideline developer on June 10, 2013.

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